REMARKS

I. Status of the Claims. By this Amendment, claims 14, 19, 20, 25, 55, 56, 72, 75, 77-80 and 83-86 are pending. Claims 14, 20, 77 and 83 have been amended to call for contacting soluble amyloid β protein in the cerebrospinal fluid (CSF) in vivo with an exogenous free end specific antibody. The specification discloses that antisenilins are secreted into the CSF where they bind to soluble Aβ peptides. *See* specification at, e.g., page 14, lines 15-17. Thus, the applications describes contacting soluble amyloid β protein in the CSF in vivo. "Exogenous" as used herein is accorded its ordinary meaning of "[d]escribing substances...that originate outside an organism." Oxford Dictionary of Biology, fourth edition, 2000, Oxford University Press at page 221 (attached herewith at Tab A). The specification sets out that free-end specific antibodies to be used in methods of treating antibodics are produced by hybridoma and/or recombinant DNA technologies. Such antibodies "originate from outside" the patient to be treated. Accordingly, such antibodies arc "exogenous." Accordingly, by this Amendment no new matter is added to the application.

II. Priority Date. In the last Office Action, the Examiner contended that the claims are not entitled to the priority date of provisional application 60/041,850, filed April 9, 1997 (the "provisional '850 application" or "'850 application") because the '850 application's disclosure was insufficient to comply with the written description and enablement requirements set forth in 35 U.S.C. §112, first paragraph. The Examiner's position is not believed to be well taken. As set forth below, the '850 application provides the requisite written description for the pending claims and also enables one of ordinary skill in the art to make and use the claimed invention without undue experimentation. The pending claims should thus be accorded the April 9, 1997 filing date of the provisional '850 application.

(i) Written Description. It is respectfully submitted that the provisional '850 application complies with the written description requirement set forth in 35 U.S.C. §112, first paragraph for the present claims. "[T]he test to determine if an application is to reccive the benefit of an earlier filed application is whether a person of ordinary skill in the art would recognize that the applicant possessed what is claimed in the later filed application as of the filing date of the earlier filed application." *Noelle v. Lederman,* 355 F.3d 1343, 1348 (Fed. Cir. 2004); *see also Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) ("[A]pplicant must also convey with

reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*.) (emphasis in original). The precise words of the claim need not be present in the application. *Fujikawa v. Wattanasin,* 93 F.3d 1559 (Fed. Cir. 1996) (Disclosure need only "reasonably convey" possession; "ipsis verbis disclosure is not necessary to satisfy the written description requirement of section 112.") The written description requirement "ensure[s] that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as detailed in the patent specification." *Reiffin v. Microsoft Corp.,* 214 F.3d 1342, 1354 (Fed. Cir. 2000). Upon reading the specification, one of ordinary skill in the art "must immediately discern the limitation at issue in the claims." *Purdue Pharma L.P. v. Faulding Inc.,* 230 F.3d 1320, 1323 (Fed. Cir. 2000).

The pending claims are directed to methods for inhibiting accumulation or neurotoxicity of Aβ in a patient by contacting soluble Aβ in the cerebrospinal fluid of the patient with a free-end specific antibody to Aβ. As argued in the previous response, the present claims are fully supported and described (in the manner set forth in 35 U.S.C. §112, first paragraph) in the '850 provisional application. That is to say, a person of ordinary skill in the art viewing the '850 application would recognize that the inventor of the claims pending in this application was in possession of the claimed invention at the time the '850 application was filed and that such claims are fully described in the '850 application. In short, a person of ordinary skill in the art would recognize that the present Applicant possessed what is claimed in the present application as of the filing date of the '850 application.

That the pending claims are described in the '850 application in the manner called for in 35 U.S.C. §112, first paragraph is established by the accompanying Declaration of Dr. Kenneth L. Rock ("the Rock Declaration"), Chairman of the Department of Pathology at the University of Massachusetts Medical Center. Since the 1970's, Dr. Rock has been engaged in studying and carrying out laboratory work on T-cell, B-cell, and antibody responses, including the mechanisms by which antibody responses are generated. Rock Declaration at paragraph 2. He has conducted research on developing therapeutic monoclonal antibodies, including using monoclonal antibodies *in vivo* to delete subsets of T-cells and NK cells, bind cell surface receptors to inhibit or stimulate immune responses and treat cancers (*id.*), and since 1994, he has worked for and consulted with companies to develop immunotherapies to treat cancers and infectious diseases, including the

use of antibodies as therapeutic agents. *Id.* at paragraph 3. Over the past 31 years, Dr. Rock has been the author or co-author of more than 120 articles in peer reviewed journals and 35 books or reviews pertaining to his work. *See* Curriculum Vitae, attached to Rock Declaration as Tab A. He is a co-inventor of six patents granted by the USPTO. *Id.*

As set forth in his accompanying Declaration, Dr. Rock studied the '850 provisional application and concluded that in April 1997, upon reading the '850 application, one of ordinary skill in the art would have understood that the inventor was in possession of the methods called for in the present claims. *See* Rock Declaration at paragraph 7. Dr. Rock reached this conclusion based on the presence in the disclosure of '850 application of information related to the production of therapeutic antibodies separate from gene therapy (Rock Declaration at paragraphs 10 and 13), the stated purpose of the antibodies as inhibiting Aβ aggregation (*Id.* at paragraph 11) and the repeated disclosure relating to providing recombinant end-specific antibody molecules to the CSF of Alzheimer's disease patient, where it could bind soluble Aβ and prevent the accumulation of Aβ. *Id.* at paragraph 12. The Rock Declaration sets forth, "Had I (or one of the post-doctoral students working with me) read the provisional ['850] application at that time [i.e., April 1997], I (and the post-doctoral student) would have recognized immediately that the inventor was in possession of a method of inhibiting the accumulation of Aβ or inhibiting the neurotoxicity of Aβ by contacting soluble Aβ in the cerebrospinal fluid of a patient suffering from Alzheimer's Disease with a free-end specific antibody to Aβ." *Id.* Dr. Rock further concluded that one of ordinary skill in the art would not conclude that the provisional '850 application is limited to using gene therapy and that, in fact, one of ordinary skill in the art would have "immediately appreciated that treatment of Alzheimer's disease by contacting soluble Aβ in the CS with a free-end specific antibody could be affected by administering such an antibody to a patient." *Id.* at paragraph 15.

Thus, the Rock Declaration establishes that the '850 application satisfies the "possession test" laid down by the courts. *Noelle,* 355 F.3d at. 1348; *Vas-Cath Inc.,* 935 F.2d at 1563-64. That is, the Rock Declaration establishes that the '850 application contains sufficient information to "reasonably convey" that the inventor was in possession of the claimed methods for inhibiting accumulation or neurotoxicity of Aβ in a patient by contacting soluble Aβ in thc cerebrospinal fluid of the patient with a free-end specific antibody to Aβ (*Id.*), that claims to such methods do not "overreach the scope of the inventor's contribution" to methods of treating

Alzheimer's disease at the time the '850 application was filed (*Reiffin,* 214 F.3d at 1354), and that one of ordinary skill in the art could "immediately discern" each limitation of the claims (*Purdue Pharma L.P.,* 230 F.3d at 1323. The written description requirement of section 112, first paragraph is satisfied, accordingly.

(ii) Enablement. Section 112, first paragraph requires that the specification set forth the invention in sufficient detail to allow one of ordinary skill in the art to "make and use the invention." The enablement requirement is satisfied if one of ordinary skill in the art can make and use the invention without "undue experimentation." *In re Wands,* 858 F.2d 731, 737 (Fed. Cir. 1988) Enablement "is not precluded even if some experimentation is necessary," so long as the amount of required experimentation is not "unduly extensive." *Hybritech Inc. v. Monclonal Antibodies, Inc.,* 802 F.2d 1367, 1384 (Fed. Cir. 1986). Satisfaction of the enablement requirement requires only objective enablement. *In re Wright,* 999 F.2d 1557, 1561 (Fed. Cir. 1993). Factors used to determine whether undue experimentation is necessary to make and use the invention include the (1) breadth of the claims, (2) nature of the invention, (3) state of the prior art,(4) level of ordinary skill in the art, (5) level of predictability, (6) amount of direction provided by the inventor, (7) existence of working examples, and (8) quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands* 858 F.2d at 737. As long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. *In re Fisher,* 427 F.2d 833, 839 (CCPA 1970); *Engel Industries, Inc. v. The Lockformer Company,* 946 F.2d 1528, 1533 (Fed. Cir. 1991) ("The enablement requirement is met if the description enables any mode of making and using the claimed invention."); *Spectra-Physics, Inc. v. Coherent, Inc.,* 827 F.2d 1524, 15341533 (Fed. Cir. 1987), *cert denied,* 484 U.S. 954 (1987) ("Nonenablement is the failure to disclose any mode...and does not depend on the applicant advocating a particular embodiment or method for making the invention.")

The Declaration of Dr. Howard J. Federoff ("the Federoff Declaration"), Executive Vice President for Health Sciences and Executive Dean of the Georgetown University Medical Center accompanies this submission.

Dr. Federoff is the Chairman of the NIH Recombinant DNA Advisory Committee (RAC) and since 1988 has conducted research in the field of gene therapy for neurodegenerative

diseases, including Alzheimer's disease. Federoff Declaration at paragraphs 2-4. Dr. Federoff is the author or co-author of more than 150 peer reviewed articles and/or invited reviews, monographs, book chapters and editorials pertaining to his work in the field of neurodegenerative diseases, including Alzheimer's disease (*See* Curriculum Vitae, attached to Federoff Declaration as Tab A), and he has participated in clinical studies of treatments for human degenerative diseases (Federoff Declaration at paragraphs 3-4).

The Federoff Declaration reports that "no later than April 9, 1997 [i.e., the filing date of the provisional '850 application], the information disclosed in the '850 application and the techniques that were then well known to those working in the field of gene therapy would have been sufficient to enable a person of ordinary skill in the field of gene therapy to use gene therapy to practice the methods called for in the pending claims of the present application for inhibiting accumulation or neurotoxicity of Aβ by contacting soluble Aβ in the CSF of a patient suffering from Alzheimer's Disease with a free-end specific antibody to Aβ." Federoff Declaration at paragraph 10.

Presented below is an analysis of the present claims in view of (a) the factors set forth in *in re Wands* and (b) the information reported in the Federoff Declaration.

(1) The breadth of the claims. The claims are narrowly drawn to inhibiting the accumulation of Aβ peptide in the brain of a patient suffering from Alzheimer's disease or inhibiting the neurotoxicity of amyloid β peptide in a patient suffering from Alzheimer's disease by contacting soluble amyloid β peptide in the cerebrospinal fluid of the patient with an exogenous free-end specific antibody which is targeted to a free N-terminus of amyloid β peptide or a free C-terminus of amyloid β peptide Aβ1-40. Thus, the claims are directed to treating specific conditions, i.e., accumulation of Aβ peptide in the brain and neurotoxicity of amyloid β peptide in Alzheimer's disease, with a specific therapeutic agent, i.e., the aforementioned end-specific antibody.

(2) The nature of the invention. The nature of the invention is treatment of Alzheimer's disease. The provisional '850 application discloses gene therapy as a means to provide an end-specific antibody to Aβ to the CSF, where it would contact Aβ leading to clearing of Aβ from the CSF and prevention of amyloid plaques. The Federoff Declaration reports that upon

secretion by neuronal cells, an end-specific antibody would diffuse in the CSF and bind Aβ peptides. Federoff Declaration at paragraph 18.

(3) State of the prior art. The Federoff Declaration sets forth that as of April 1997, the prior art had established the role of Aβ in Alzheimer's disease (*id.* at paragraph 13.i), had demonstrated that monoclonal antibodies inhibit fibrillar aggregation of Aβ peptides(*id.* at paragraph 13.ii), had identified AAV as a preferred vector for gene delivery to the nervous system(*id.* at paragraph 13.iii), and had developed stereotactic surgery as a means to deliver therapeutic agents to the brain (*id.* at paragraph 13.iv).

(4) The level of skill in the art. The Federoff Declaration reports that the level of skill in the art of gene therapy in April 1997 was "extremely high." *Id.* at paragraph 11.

(5) Predictability/unpredictability of the art. The Federoff Declaration reports that by 1996 the predictability of using gene therapy to treat disease had progressed to the point that a chapter on gene therapy was included in Goodman & Gilman's: The Pharmacological Basis of Therapeutics, a standard reference book on therapeutics (*id.* at paragraph 21) and that this chapter reported that between 1990 and 1994 the NIH RAC had approved 58 gene therapy clinical trials (*id.*). With respect to gene therapy to treat Alzheimer's disease, the Federoff Declaration sets forth that "the level of understanding of Alzheimer's disease, the level of skill in the art for neurological diseases, and the amount of guidance in the '850 application provide a rational, predictable basis for using the methods for treating Alzheimer's called for in the claims pending in this application" *(id.* at paragraph 12) and that "all of the technology for successful gene therapy in the brain was available in 1997" (*id.* at paragraph 22). Dr. Federoff concludes, "In short, by April 1997 it was entirely predictable by those skilled in the art of gene therapy that free end-specific antibodies to Aβ could be used in gene therapy approaches to treat Alzheimer's disease. I am aware of no facts that would lead me to reach a contrary conclusion." *Id.*

(6) The amount of direction provided by the inventor. As set forth in the Federoff Declaration, the provisional '850 application "provides an abundance of guidance for production of an end-specific antibody to Aβ for use in a treatment for Alzheimer's disease." *Id.* at paragraph 14.

Dr. Federoff noted guidance pertaining to generating end-specific antibodies (*id.* at paragraph 15), choosing a vector and producing constructs to express the end-specific antibodies, particularly scFv constructs in neuronal tissue (*id.* at paragraph 16), obtaining a high titer recombinant virus stock (*id.* at paragraph 17), and delivering vectors expressing recombinant vectors to the central nervous system (*id.* at paragraph 18).

(7) The existence of working examples. The '850 application sets forth a prophetic example in a mouse model of Alzheimer's disease. *See* provisional '850 application at pages 43-46. This provides a useful, practical guide for practicing the invention.

(8) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. The Federoff Declaration sets forth that "No further information beyond that given in the specification [of the provisional '850 application] would have been needed to enable a worker in the gene therapy to practice the methods called for in the presently pending claims." *Id.* at paragraph 20.

The analysis of the Wands factors in view of the Federoff Declaration thus establishes that the '850 provisional application contains sufficient information to enable one of ordinary skill in the gene therapy field to (i) generate end-specific monoclonal antibodies to Aβ, (ii) place the immunoglobulin genes encoding such antibodies in a viral vector that will allow the genes to be expressed in the nervous system and secreted into the CSF, (iii) obtain a high titer of recombinant virus and (iv) deliver it to the nervous system, where (v) the recombinant virus will infect neuronal tissue, then (vi) be expressed and secreted into the CSF, where (vii) it will bind soluble Aβ. As set forth in the Federoff Declaration, "No further information beyond that given in the specification would have been needed to enable a worker in the field of gene therapy field to practice the methods called for in the presently pending claims." It is thus evident that it would not take undue experimentation to make and use the presently claimed invention. Based on the information set forth in the Federoff Declaration standing alone, the present claims satisfy the enablement requirement of section 112, first paragraph.

As set forth respectively in the Rock and Federoff Declarations, the '850 provisional application contained sufficient information to (a) demonstrate to one of ordinary skill in the art that the inventor had possession of the invention called for in the present claims and (b) enable one of ordinary skill in the art to make and use the invention called for in the present claims without undue experimentation. Thus, the provisional '850 application complies with all the requirements under section 112, first paragraph, with respect to the pending claims. Accordingly, the pending claims are entitled the April 9, 1997 filing date of the '850 application. The Examiner is respectfully requested to acknowledge the April 9, 1997 filing date of the application.

III. Claim Rejections. The claim rejections set forth in the Office Action are summarized and addressed as follows.

(i) Rejections Under 35 U.S.C. §102.

(a) Claims 14, 19, 20, 25, 55, and 56 remain rejected as allegedly anticipated under section 102(b) by Bard et al., *Nature Med.* 6:916-919 (2000), as evidenced by Su et al., *J. Neurosci. Res.* 53:177-186 (1998) and Frenkel et al., *J. Neuroimmunol.* 88:85-90 (1998). As set forth above in section II, the pending claims are entitled to a priority date of April 9, 1997. Bard was published in August 2000, i.e., after the priority date of the amended claims. Accordingly, Bard is not prior art to the pending claims. Thus, the present rejection should be withdrawn.

(b) Claims 14, 19, 20, 25, 55, 56, 72, 75, 77, 80, 83 and 86 remain rejected under section 102(e) as anticipated by Schenk, U.S. Patent No. 6,787,637. As set forth above in section II, the pending claims are entitled to a priority date of April 9, 1997. Schenk has an earliest claimed priority date of May 28,1999, i.e., after the priority date of the pending claims. Accordingly, Schenk is not prior art to the pending claims. Thus, the present rejection should be withdrawn.

(ii) Rejections Under 35 U.S.C. §103.

Claims 78, 79, 80 and 84 remain rejected as allegedly obvious over Schenk in view of Saido et al., *Neurosci. Lett.* 215:173-176 (1996) and Harigaya et al., *Biochem. Biophys. Res.*

Comm. 276:422-427 (2000). For the reasons set forth immediately above, neither Schenk nor Harigaya is prior art to the pending claims. Thus, the present rejection should be withdrawn.

(iii) Rejections Under 35 U.S.C. § 112, second paragraph

Claims 14, 20, 77 and 83 are rejected as indefinite for allegedly being incomplete for omitting essential steps that amount to a gap between the steps. The Examiner's initial assertion is that the omitted essential step is delivery of a free-end specific antibody to a patient. *citing* MPEP 2172.01. This is traversed on the grounds that MPEP 2172.01 does not set forth that a claim that omits an cssential step should be rejected as indefinite. MPEP 2172.01 sets forth that a "claim that omits matter disclosed to be essential to the invention disclosed in the specification may be rejected under 35 U.S.C. 112, first paragraph, as not enabling." *(citation omitted)*. Thus, the initial stated rationale for the instant rejection is improper. For at least this reason, the rejection should be removed. It is also noted that a rejection under section 112, first paragraph would be improper, becausc the specification does not disclose administration to be an essential step.

In further response and without conceding the validity of the rejection, claims 14 and 16 have been amended to call for "contacting in vivo soluble amyloid β peptide in the cerebrospinal fluid of said patient with an exogenous free-end specific antibody." The amendments are believed to address the Examiner's ground for rejection. The amended claims are not lacking an essential step. As set forth in the accompanying Federoff Declaration, upon contacting soluble Aβ in the CSF, the exogenous free-end specific antibody will bind to Aβ and have the desired effect of inhibiting accumulation of amyloid β peptide in the brain (claim 14) or inhibiting the neurotoxicity of amyloid β peptide (claim 16). *See* Federoff Declaration at paragraph 15. No further steps are required. Moreover, claims 14 and 16 each include a single step of "contacting soluble amyloid β peptide in the cerebrospinal fluid of said patient with an exogenous free-end specific antibody which is targeted to a free N-terminus of amyloid β peptide or a free C-terminus of amyloid β peptide Aβ1-40." A method comprising a single step cannot "[fail] to interrelate essential elements of the invention." *See* MPEP 2171.01. For these additional reasons, the present rejection should be withdrawn.

The Examiner further takes the position that without a delivery or administration step the claims read on a patient's own auto-antibodies. In response, as noted above, the claims have been amended to call for an exogenous antibody. Thus, the claims cannot be construed as reading upon auto-antibodies.

The Examiner further asserts that it is unclear whether the contacting called for in the claims occurs in vivo or ex vivo. In response, without conceding the validity of the Examiner's position, the claims have been amended to call for "contacting in vivo."

For at least the reasons set forth above, the pending claims comply with the strictures of section 112, second paragraph. The scope of the claims is clear, so the public is informed of the claim boundaries to enable assessment of activities that would constitute infringement. Reconsideration of the claims and withdrawal of the indefiniteness rejection is respectfully requested.

IV. Conclusion. In view of the above amendment, it is respectfully submitted that the subject application is in condition for allowance. If the Examiner believes there are issues remaining that could be resolved by an Examiner's Amendment, the Examiner is invited to contact the undersigned attorney for a telephonic interview.

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Respectfully submitted,

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